Applicants previous arguments are not mooted by the new ground of rejection because the newly cited reference Cantor does nothing to remedy the deficiencies previously noted in Skiena and Futreal. If the rejection is to be maintained the Examiner is expressly requested to address these deficiencies as noted below.

In brief, the Examiner's proposed combination of Skiena with either Futreal and/or Cantor does not result in a modification of Skiena's method to include a step of designing a probe array to comprise a probe set complementary to a known reference sequence. The Examiner relies on Futreal to establish that target sequences that are variants of a reference sequence are known to exist and it is useful to analyzed them with probe based assays. However, merely performing Skiena's method with a target sequence that happens to be a variant of a known reference sequence changes the use but not the design of Skiena's array. Thus, Futreal does not remedy the deficiency in Skiena's design of an array. Cantor is merely cited as discussing use of less than a complete array of probes; not design of an array to analyze a target sequence that is a variant of a known gene. Cantor does not therefore remedy the deficiencies of either Skiena or Futreal in this regard. Thus, the proposed combination of references does not result in the step of designing an array of probes to analyze a target sequence that is a variant of a known gene, as claimed.

To derive this step from the cited references one would not only have to perform Skiena's method with a target sequence that is a variant of a known reference sequence, one would at the very least have to discard Skiena's own strategy of starting with a universal sequence array containing all probes of a given length in favor of designing an array to comprise a set of probes having complementarity to the known reference sequence. To do so would forfeit the utility of Skiena's own method for an analyzing any kind of target sequence. Moreover, the remaining steps in Skiena method which are intended for analyzing a target sequence without any prior knowledge as to its identity would seem unnecessarily complex for the simpler task of analyzing a variant of a known sequence. The Futreal reference merely indicates the well-known fact that target sequences that are variants of known reference sequences exist; it does not provide any

suggestion to modify the strategy for analyzing target sequences proposed by Skiena, and particularly not in a way that forfeits the principal advantage of Skiena's method. Likewise, Cantor proposes analyzing rare target sequences as an advantage of his own methods, but does not provide any suggestion to modify the strategy for analyzing target sequences proposed by Skiena, and particularly not in a way that forfeits the principal advantage of Skiena's method. Thus, there was no motivation to combine the references in a manner that results in the claimed invention.

Applicants also previously pointed out that Skiena does not discloses 'estimating," or "reestimating" a target sequence, much less "reestimating" the sequence until it remains constant between successive cycles. Neither Futreal nor Cantor remedies this deficiency. The Examiner appears to take the view that simply determining a set of hybridizing oligonucleotides itself constitutes "estimating the sequence of a target," under a broad interpretation of the claims which the Examiner feels entitled to make during prosecution. In response, applicants submit that the Examiner is not merely interpreting the claims broadly, but effectively reading out explicitly recited claim steps. The present claims recite separate steps of "determining the relative hybridization of the probes to the target nucleic acid," and "estimating the sequence of the target nucleic acid from the relative hybridization of the probes." Thus, to view "determining the relative hybridization of probes" as being equivalent to estimating a sequence effectively reads out the step of "estimating the sequence" from the claim. Accordingly, Applicants maintain that Skiena does not teach 'estimating," or "reestimating" a target sequence, much less "reestimating" the sequence until it remains constant between successive cycles.

The distinction based on Skiena's lack of disclosure of "estimating" a sequence is all the more evident in dependent claim 13. This claim recites that the step of "estimating" includes "repeating (a) and (b) until each nucleotide of interest in the sequence of the target nucleic acid has been estimated." In Skiena's initial iterations of his method, he does not disclose estimating a target sequence but rather identifies a subset of hybridizing probes, which is used to design a second set of probes. In the final

step of Skiena's method he does not estimate a target sequence, but rather determines the sequence uniquely. In Skiena's view at least, the determined sequence is correct and not an estimated, much less a reestimated sequence (col. 7, lines 12-15). Therefore, Skiena does not estimate each nucleotide of interest in a target sequence, as recited in claim 13.

5. Claims 7-14 stand rejected under 35 USC 103 as obvious over Skiena in view of Futreal in further view of Cantor in further view of Cronin. This rejection is traversed for at least the same reasons as given above an in response to previous office actions.

6. Claims 3 and 4 stand rejected as obvious over Skiena in view of Futreal in further view of Cantor in further view of Horwitz. This rejection is traversed for at least the same reasons as given above an in response to previous office actions.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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